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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/227,687	01/08/1999	FRANCIS P. TALLY	CPI98-03P9MA	7885

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CUBIST PHARMACEUTICALS, INC.
65 HAYDEN AVENUE
LEXINGTON, MA 02421

EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/227,687	TALLY ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- Th MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *67-96 and 119-131* is/are allowed.

6)☒ Claim(s) *97-112 and 114* is/are rejected.

7)☒ Claim(s) *113 and 115-118* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/21/2003 has been entered.

Receipt is acknowledged of an amendment, filed 11/21/2003, in which several amendments were made to the claims (claims 67, 69, 71, 77, 84, 86, 88, 92). Claims 67-131 are pending in the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 97-98, 100, 106-107, 111-112, 114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bostian et al (WO 96/40979, 19 December 1996; see the entire document) in view of Setterstrom et al (U.S. Patent No. 6,309,669 B1; see the entire patent). **This is a new rejection.**

Bostian et al teach methods for evaluating microbial genes as targets for compounds that inhibit the pathogenesis of a microbe, and for evaluating the expected therapeutic effect of compounds that inhibit a reaction of a microbial cell that is related to the expression of a specific gene (i.e. the "gene target" of the instant invention). The methods utilize recombinant microbes which contain DNA constructs or alterations (i.e. the "switches" of the Bostian et al application) that allow the level of activity of the products of coding regions associated with those constructs or alterations to be controlled by the presence or absence of a specific small molecule or "switching compound" at any of several points in the infection process (e.g. Abstract; page 17, lines 3-21; page 4, lines 4-19). The expression of the coding regions associated with the DNA constructs or alterations is designed to affect the activity of the specific gene target in the microbe while the microbe is in the process of infecting a host organism. The methods comprise infecting an animal or plant model host with a genetically altered microbe where the genetic alteration causes a change in the level of activity of a product of the coding sequence of a putative pathogenesis gene or essential gene in the microbe in response to an environmental change (e.g. exposure to a switching compound) and determining whether the state of infection or condition of the host is changed as a result of altering the level of activity of the target gene or

gene product. In some cases the level of activity of the target gene is affected by the administration of the switching compound to the host animal.

The DNA constructs or "alterations" used in the invention taught by Bostian et al comprise repressor/operator pairs used as regulatory "switches" to control expression of a coding sequence that affects the functional activity of the target gene (e.g. Figure 3; page 41 lines 3-29). A preferred switching compound of the system is tetracycline, used in conjunction with a promoter operatively linked to operator sequences (i.e. tetO) that specifically bind to the tetracycline repressor (tetR) (e.g. page 17, lines 3-21; page 41, lines 3-29; page 54, lines 15-17). A switching compound of the invention can cause a decrease or an increase in the level of activity of a coding sequence, depending upon the type of DNA construct or alteration used (e.g. sense or antisense expressed and the type of repressor/operator construct) (e.g. pages 56-57). The small molecule-responsive "switches" of the invention can be directly linked to an endogenous target gene of interest (e.g. by integration of a switch construct into a bacterial chromosome such that a chromosomal gene is now responsive to the small molecule "switcher") or indirectly linked by a second repressor/operator element (e.g. Figure 3; page 7, lines 1-17; page 29, lines 12-16).

In the methods taught by Bostian et al, the putative pathogenesis gene or essential gene is a valid target if the state of the infection or the physiological condition of the host is altered in response to the change in level of activity of the target gene (e.g. page 5, lines 16-35). Criteria for evaluation in the host include the ability of the microbe to replicate (the test gene expression can be "on" or "off"), the ability to produce specific exoproducts involved in virulence of the organism, and the ability to cause symptoms of disease in the animals (e.g. page 49, lines 14-19).

Acceptable mammalian animal models for use in the system include mice, rats, rabbits, dogs, cats and swine (e.g. page 13, lines 24-27; Examples 5-10). Microbes that can be used in the methods described by Bostian et al include bacteria, protozoa, fungi, yeast and viruses. Staphylococcus aureus is a bacterial microbe described as useful in the methods of the invention (page 14, lines 9-14). Bostian et al teach several different specific animal model systems for studying the effects of altering gene expression on infection of a host animal by a microbe (e.g. the Mouse Soft Tissue Model, the rabbit Osteomyelitis model, etc.; see Examples 5-10).

In an exemplified embodiment taught by Bostian et al, the expression of an exogenous lacI repressor results in the repression of synthesis of an altered endogenous virulence gene, resulting in a loss of virulence (Figure 3). In this embodiment, the lacI repressor binds its cognate operator sequence (i.e. the "target component") and regulates the expression of a virulence gene, resulting in inhibition of virulence for pathogenic cell transplanted into a host organism. In this case, the lacI repressor acts as would the test protein in the rejected claims that is shown to inhibit growth rates for the host cells.

Bostian et al do not explicitly teach the use of control animals in their methods where the target gene function in the infecting microbe has not been inhibited (i.e. a "normal" infection control).

Setterstrom et al teach the use of novel burst-free, sustained release biocompatible and biodegradable microcapsules that can be programmed to release their active core (e.g. an antibiotic) for variable durations ranging from 1-100 days in an aqueous physiological environment (e.g. the Abstract). Setterstrom et al teach a set of examples wherein the rabbit osteomyelitis animal model system is used to demonstrate the efficacy of their invention (e.g.

Section VII, Examples 1-7 beginning at column 40 and continuing through column 45, line 60). In these examples, Staphylococcus aureus preparations were used to infect the tibial metaphysis of laboratory rabbits (e.g. Example 1). Antibiotic therapy using the compositions of the Setterstrom et al invention was initiated immediately or delayed for 7-days. For each infected animal the infected tibia was harvested and used to determine the extent of infection (e.g. Example 6). Whether treatment was initiated immediately or postponed for seven days post-infection, the experiments were conducted with control animals that were infected with S. aureus and received no antibiotic treatment (e.g. Examples 3 & 4).

It would have been obvious to one of ordinary skill in the art at the time of applicants' invention to modify the methods taught by Bostian et al for the characterization of potential antimicrobial gene targets to include the use of control animals where the activity of the gene target is not inhibited because Bostian et al teach it is within the skill of the art to utilize a tetracycline-responsive system to control the level of activity of a gene target in a microbe during the process of infection and because Setterstrom et al teach it is within the skill of the art to utilize a control animal to provide a clear contrast between treatment or nontreatment of infection. One would have been motivated to do so in order to receive the expected benefit, as exemplified by Setterstrom et al, of being able to compare the level of infection in an animal in which no target gene has been inactivated with an animal in which at least one gene function has been altered (e.g. the animals treated with antibiotics as taught by Setterstrom et al). Absent any evidence to the contrary, there would have been a reasonable expectation of success in using a control animal, as taught by Setterstrom et al, in the methods taught by Bostian et al to provide a clear background for comparison of the effects of target gene inactivation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 97-110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection.**

There is no clear and positive prior antecedent basis in claim 97 for the term "biomolecule".

Conclusion

Claims 97-112 and 114 are rejected. Claims 113 and 115-118 are objected to as being dependent upon a rejected claim. Claims 67-96, 119-131 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

GERRY LEFFERS
PRIMARY EXAMINER